

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

In its capacity as elected Office

Date of mailing (day/month/year) 13 May 1998 (13.05.98)	Applicant's or agent's file reference H 1596-1 WO
International application No. PCT/SE97/01604	Priority date (day/month/year) 08 October 1996 (08.10.96)
International filing date (day/month/year) 24 September 1997 (24.09.97)	
Applicant LOFROTH, Jan-Erik et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

07 April 1998 (07.04.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For re g Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) H 1596-1 WO

Box No. I TITLE OF INVENTION
PHARMACEUTICAL COMPOSITIONS

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

ASTRA AKTIEBOLAG
S-151 85 SÖDERTÄLJE
Sweden

☐ This person is also inventor.

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.
19237 ASTRA S

State (i.e. country) of nationality: SE

State (i.e. country) of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

LÖFROTH, Jan-Erik
Ringleken 13
S-431 69 MÖLNDAL
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: SE

State (i.e. country) of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Patent Department
Astra Aktiebolag
S-151 85 SÖDERTÄLJE
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.
19237 ASTRA S

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

ÖDMAN, Jonas
Kullegatan 3A
S-412 62 GÖTEBORG
Sweden

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

SE

State (i.e. country) of residence:

SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LV Latvia |
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| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | |
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| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> KE Kenya | |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> VN Viet Nam |
| | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KR Republic of Korea | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet: |
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| <input checked="" type="checkbox"/> LR Liberia | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> LS Lesotho | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> LT Lithuania | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> LU Luxembourg | <input type="checkbox"/> |

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) Sweden	(08 October 1996) 08.10.1996	9603667-8	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / SE

Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office): Sweden Date (day/month/year): 07 May 1997 (07.05.1997) Number: SE96/01092

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

- 1. request : 4 sheets
- 2. description : 16 sheets
- 3. claims : 2 sheets
- 4. abstract : 1 sheets
- 5. drawings : 2 sheets

Total : 25 sheets

This international application is accompanied by the item(s) marked below:

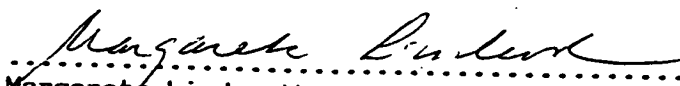
- 1. ☒ separate signed power of attorney
- 2. ☒ copy of general power of attorney
- 3. ☐ statement explaining lack of signature
- 4. ☐ priority document(s) identified in Box No. VI as item(s):
- 5. ☒ fee calculation sheet
- 6. ☐ separate indications concerning deposited microorganisms
- 7. ☐ nucleotide and/or amino acid sequence listing (diskette)
- 8. ☒ other (specify): ITS SE 96/01092

Figure No. 1 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 23 September 1997



Margareta Linderöth
Patent Department, Astra Aktiebolag

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1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 1(2):	
5. International Searching Authority specified by the applicant: ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

Date of receipt of the record copy by the International Bureau:

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08/945655
(16x1)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D	15 FEB 1999
WIPO	

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 1596-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE97/01604	International filing date (day/month/year) 24.09.1997	Priority date (day/month/year) 08.10.1996
International Patent Classification (IPC) or national classification and IPC ₆ A 61 K 9/20 A 61 K 31/19		
APR 5 1999 GROUP 1800		
Applicant ASTRA AKTIEBOLAG et al		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
These annexes consist of a total of _____ sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 07.04.1998	Date of completion of this report 05.02.1999
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Anneli Jönsson Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE97/01604

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

- ☒ the international application as originally filed.
- ☐ the description, pages _____, as originally filed,
 pages _____, filed with the demand,
 pages _____, filed with the letter of _____,
 pages _____, filed with the letter of _____.
- ☐ the claims, Nos. _____, as originally filed,
 Nos. _____, as amended under Article 19,
 Nos. _____, filed with the demand,
 Nos. _____, filed with the letter of _____, **APR 5 1999**
 Nos. _____, filed with the letter of _____, **GROUP 1800**
- ☐ the drawings, sheets/fig _____, as originally filed,
 sheets/fig _____, filed with the demand
 sheets/fig _____, filed with the letter of _____,
 sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE97/01604

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-13

because:

☒ the said international application, or the said claims Nos. 12-13
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1(iv):Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE97/01604

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-11</u>	YES
	Claims		NO
Inventive step (IS)	Claims	<u>1-11</u>	YES
	Claims		NO
Industrial applicability (IA)	Claims	<u>1-11</u>	YES
	Claims		NO

2. Citations and explanations

The claimed invention pertains to a pharmaceutical composition comprising the HMG-CoA-reductase inhibitor fluvastatin. Fluvastatin is a water soluble drug with a high solubility in water (>30 mg/ml in water at 37 °C). The invention provides a pharmaceutical composition comprising a water soluble salt of fluvastatin. The composition can be selected from the group matrix formulations (eroding or non-eroding), diffusions-controlled membrane coated formulations and combinations thereof.

Document US 5 356 896 A discloses a stabilised pharmaceutical composition comprising the HMG-CoA reductase inhibitor fluvastatin. The composition comprises fluvastatin in intimate contacting association with an "alkaline stabilising medium" to achieve optimal stability of the medicament. The dosage form can be coated with a film or be coated with an enteric layer. The composition disclosed is not a composition with a sustained release of the fluvastatin. The composition disclosed disintegrates fast and provides a rapid intestinal absorption of the drug. The film-coated tablet has a disintegration time of about 10 to 30 minutes. The enteric coated tablet has a disintegration time if about 30 to about 6 hours, the enteric layer is applied to protect against premature degradation of the drug prior reaching the intestinal absorption site. The document does not disclose a composition administering fluvastatin with a sustained release. The document only discloses the general state of the prior art.

.../...

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE97/01604

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V.

Document EP 465096 A1 discloses a composition with time controlled administration of an HMG-CoA reductase inhibitor. The time controlled administration (time-controlled administration during 6-24 hours) is achieved by, for example, diffusion controlled systems, osmotic devices, dissolution controlled matrices and erodible/degradable matrices. The dosage form disclosed comprises a HMG-CoA reductase inhibitor, for example, simvastatin or lovastatin, in a matrix of hydroxypropyl methyl cellulose (as is preferred in the present claim 4). A composition comprising fluvastatin is not disclosed. The solubility of fluvastatin is different from the solubility of lovastatin or simvastatin. The water solubility at pH 5.0 at room temperature for lovastatin and simvastatin and at pH 6.0 for fluvastatin has been measured. The volume of water required to dissolve a 20 mg dose of lovastatin, simvastatin and fluvastatin sodium is 15385, 14286 and 10 ml, respectively. Therefore, it is not obvious to a person skilled in the art to include fluvastatin in the dosage form disclosed in the document EP 465096 to obtain a composition with a sustained release of fluvastatin. Consequently, the document only discloses the general state of the prior art.

Therefore, the invention according to claims 1-11 is considered to fulfil the requirements of novelty, inventive step and industrial applicability.

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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61K 9/20, 31/19</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/15264 (43) International Publication Date: 16 April 1998 (16.04.98)</p>
<p>(21) International Application Number: PCT/SE97/01604 (22) International Filing Date: 24 September 1997 (24.09.97) (30) Priority Data: 9603667-8 8 October 1996 (08.10.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LÖFROTH, Jan-Erik [SE/SE]; Ringleken 13, S-431 69 Mölndal (SE); ÖDMAN, Jonas [SE/SE]; Kullegatan 3A, S-412 62 Göteborg (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PHARMACEUTICAL COMPOSITIONS FOR SUSTAINED RELEASE OF THE HMG-CoA REDUCTASE INHIBITOR FLUVASTATIN</p> <p>(57) Abstract</p> <p>The present invention relates to pharmaceutical compositions for sustained release comprising a water-soluble salt of the HMG-CoA reductase inhibitor fluvastatin as active ingredient, said composition being selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.</p>		

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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PHARMACEUTICAL COMPOSITIONS FOR SUSTAINED RELEASE OF THE HMG-CoA REDUCTASE INHIBITOR FLUVASTATIN

TECHNICAL FIELD

5 The present invention relates to pharmaceutical compositions for sustained release comprising a water soluble salt of the HMG-CoA reductase inhibitor fluvastatin as active ingredient, said composition being selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.

10

BACKGROUND ART

Sustained-release compositions

15

In recent years there has been a large increase in the development and use of sustained-release tablets which are designed to release the drug slowly after ingestion. With these types of dosage forms, the clinical utility of drugs can be improved by means of improved therapeutic effects, reduced incidence of adverse effects and simplified dosing regimens.

20

A sustained-release tablet releases the drug during several hours, typically more than 3 hours and less than 30 hours. Other commonly used terms such as "controlled release", "extended release", "prolonged release", etc., all comply with the definition of a product that releases the drug typically over more than 3 hours.

25

Several different types of formulations exist to obtain sustained release of a drug. The different formulations all aim to have release of the drug from the formulation, rather than the absorption process of the drug, as the rate limiting step. For this purpose, approaches based on the control of, e.g., dissolution,

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diffusion, swelling, osmotic pressure, complexation, ion-exchange, etc., can be employed. The actual approach taken for a given drug depends *inter alia* on the physical chemical properties of the drug. One of these is the solubility of the drug, which has a major impact on the pharmaceutical formulation strategy. A high
5 solubility of the drug substance may induce problems, as discussed further below. However, in general, sustained release can be obtained according to the following principles, or combinations of them:

(i) By formulating the drug in an insoluble matrix. The gastrointestinal fluid

10 penetrates the matrix, the drug is dissolved and diffuses out of the matrix and is absorbed. The driving force for diffusion is the concentration of the drug in the aqueous solution created by the penetrating gastrointestinal fluid. Thus, the higher the solubility, the higher the aqueous concentration of the drug in the matrix, and the faster the diffusional transport of the drug out of the matrix. If the
15 matrix is a swelling matrix, e.g. a crosslinked (ionic) polymer with entrapped solid drug, the swelling kinetics of the matrix, the dissolution rate of the drug, and the diffusion of the drug will all contribute to the overall release rate. However, if the solubility of the drug is high, the release rate will be characterized by the diffusional transport after an initial swelling has occurred.

20 A similar principle applies when drug particles or cores containing the active drug are coated with an insoluble but porous membrane of polymers. In this case, the gastrointestinal fluids penetrates the membrane, the drug is dissolved and thereafter diffuses out of the coated particle through the membrane. The driving
25 force for diffusion is the concentration of the drug in the aqueous solution created by the penetrating gastrointestinal fluid. Thus, the higher the solubility, the higher the aqueous concentration of the drug in the matrix, and the faster the diffusional transport of the drug over the membrane. It can be argued that the transport rate with this type of formulation is dictated by the pores in the membrane.

30 Nevertheless, it is the solubility which creates a high concentration gradient over

the membrane and which then is important for the transport rate from the formulation.

(ii) By formulating the drug in an eroding matrix of, e.g. a soluble polymer. The rate with which the drug will be available at the absorption site is for these matrices a combination of the swelling and erosion rates of the matrix, and the dissolution and diffusion rates of the drug. A formulation based on this principle for a soluble drug might not show acceptable sustained release due to the high concentration gradient of the drug that can be created after an initial swelling of the polymer, leading to a diffusional transport of the drug instead of a release controlled by the erosion, i.e. the dissolution of the polymer.

(iii) Release controlled by osmotic pressure, whereby a semipermeable membrane is placed around a tablet or drug particle which allows transport of water into the formulation by osmosis. As a result of increased internal pressure when the drug dissolves, drug solution is then pumped out of the tablet through a small hole in the coating. The size of the orifice in the coating controls both the volume flow into the core reservoir, and the drug solution release rate. If the drug has a high solubility, the size of the orifice must be made small to prolong the release rate. This might then create problems with the possible build up of a high hydraulic pressure inside the device until the walls ruptures.

Improved drug delivery by sustained release has been discussed more extensively in the literature, e.g. in:

- Langer and Wise (Eds.) "Medical Applications of Controlled Release", vols I and II, CRC Press Inc, Boca Raton, 1984;
- Robinson and Lee (Eds.) "Controlled Drug Delivery - fundamentals and applications", Marcel Dekker, NY, 1987;
- Bogentoft and Sjögren, in "Towards Better Safety of Drugs and Pharmaceutical Products" (Ed: Breimer), Elsevier, 1980.

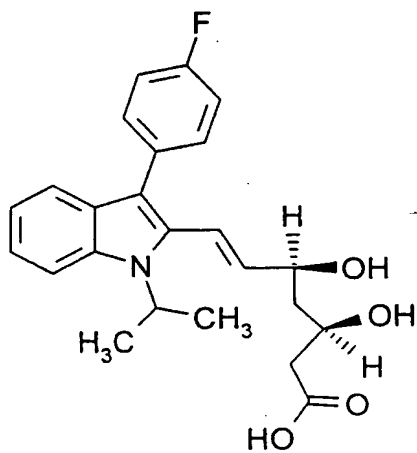
As mentioned above, the drug release from sustained release formulations is related to the drug solubility. The higher the water solubility of the drug, the faster the drug release and the shorter the duration of drug delivery. A fast release of the drug might mean that the desired rate and duration can not be obtained and that the beneficial effects of sustained release administration are lost. Thus, a special challenge is met when trying to formulate water soluble substances for sustained release formulations. One way to try to solve this problem would be to include large amounts of slow release excipients in the formulation. However, this approach has drawbacks such as increased costs and increased size of the formulation. Increased physical size of the dosage form may present problems for some patients, since the tablet will be more difficult to swallow. Another possibility is to use a less water soluble salt. However, such a change requires a more extensive development work and may also lead to bioavailability problems due to incomplete dissolution.

HMG-CoA Reductase Inhibitors

Hypercholesterolemia is related to an increased risk of coronary heart diseases. A possible way to reduce cholesterol levels in a patient is to inhibit the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, which is a key enzyme in the regulation of cholesterol biosynthesis. The HMG-CoA reductase inhibitors constitute a well known group of therapeutic agents for the treatment of hypercholesterolemia, which group comprises fermentation products such as lovastatin and pravastatin, as well as semi-synthetic analogs such as simvastatin. More recently have completely synthetic drugs, e.g. fluvastatin, been developed.

The use of some HMG-CoA reductase inhibitors for the preparation of a medicament adapted for time-controlled administration is disclosed in EP-B-0 375 156.

Fluvastatin (R*, S*-(E)-(±)-7-[3-(4-fluorophenyl)-1-(1-methyl-ethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid) is known from EP-A-0 114 027.



fluvastatin

Fluvastatin is a water soluble drug. For example, the solubility of the sodium salt of fluvastatin in water extends to more than 50 g/l. Biopharmaceutical requirements of a sustained release product of this water soluble drug would then at first sight impose formulation problems, as discussed above. Thus, with a diffusion controlled release device for this soluble substance, e.g. an insoluble matrix of a polymer, fast release rates can be expected due to the high solubility of fluvastatin creating high concentration gradients as the driving force for diffusion out of the matrix.

Second, an eroding matrix of fluvastatin is not expected to be useful due to the high concentrations of the drug in solution that can be the result when the gastrointestinal fluid penetrates the matrix. The erosion of the matrix, e.g. by dissolution of the outer hydrated polymer layers, would then indeed not be a rate controlling factor, except perhaps only for a first initial short time during hydration and swelling of the matrix.

Finally, advanced techniques with high production costs are expected to be necessary to produce osmotic pressure controlled formulations. The high solubility of fluvastatin is also expected to complicate the action of such formulations. Thus, a small orifice would be needed in order to keep the rate low with which the amount of drug is pumped out through such devices. With a small orifice, however, the hydrostatic pressure that will be built up would put demands on the choice of a strong polymer membrane.

Consequently, there is a need for pharmaceutical formulations of HMG-CoA reductase inhibitors which avoid the above mentioned drawbacks and are possible to prepare, e.g., without including large amounts of slow release excipients or the use of highly advanced techniques. Preferably, the production costs of the formulations should be low.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: Release of fluvastatin and methylparaben, and tablet erosion, from sustained-release tablets based on polyethylene oxide (PEO) 8,000,000.

Fig. 2: Release of fluvastatin, methylparaben and diclofenac from sustained-release tablets based on xanthane.

Fig. 3: Release of fluvastatin and methylparaben from sustained-release tablets based on paraffin, and release of fluvastatin from immediate release (IR) capsules.

Fig. 4: Release rate of fluvastatin and diclofenac over a polymeric membrane in a two-compartment cell at different concentrations in donor chamber.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that sustained-release compositions, comprising fluvastatin as a water soluble salt, exhibit particularly favorable release characteristics such as unexpectedly long duration and slow rate of drug release. In the present context, the term "water soluble" should be understood as a solubility of more than 30 mg/ml in water at +37°C.

Consequently, the present invention provides a pharmaceutical composition for sustained release comprising a water soluble salt, preferably the sodium salt, of fluvastatin as an active ingredient. The sustained-release fluvastatin compositions for which these favorable properties are obtained are selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.

The said eroding and non-eroding matrix formulations can be based on hydrophilic and/or hydrophobic matrix forming excipients. The matrix and membrane coated formulations may be monolithic, such as tablets, or in the form of multiple units administered in a tablet, capsule or sachets.

The hydrophilic or hydrophobic, eroding or non-eroding, matrix material and the material for film formation, can be, but is not limited to:

- cellulose derivatives such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, cellulose acetate butyrate, cellulose acetate phtalate, etc;
- polysaccharides, like alginate; xanthane; carrageenan; scleroglucan; pullulan; dextran; haluronic acid; chitin; chitosan; starch; etc;

- other natural polymers, like proteins (e.g. albumin, gelatine); natural rubber; etc;
- synthetic polymers, like acrylates (e.g. polymethacrylate, poly(hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(hydroxy ethyl methacrylate - co methyl methacrylate), Carbopol 934™); polyamides (e.g. polyacrylamide, poly(methylene bisacrylamide)); polyanhydrides (e.g. poly(bis carboxyphenoxy)methane); PEO-PPO block-co-polymers (e.g. poloxamers, etc); polyvinyl chloride; polyvinyl pyrrolidone; polyvinyl acetate; polyvinyl alcohol; polyethylene, polyethylene glycols and co-polymers thereof; polyethylene oxides and co-polymers thereof; polypropylene and co-polymers thereof; polystyrene; polyesters (e.g. poly(lactic acid), poly(glycolic acid), poly(caprolactone), etc, and co-polymers thereof, and poly(ortho esters), and co-polymers thereof); resins (e.g. Dowex™, Amberlite™); polycarbonate; cellophane; silicones (e.g. poly (dimethylsiloxane)); polyurethanes; synthetic rubbers (e.g. styrene butadiene rubber, isopropene rubber); etc;
- others, like shellacs; waxes (e.g. carnauba wax, beeswax, glycowax, castor wax); nylon; stearates (e.g. glycerol palmitostearate, glyceryl monostearate, glyceryl tristearate, stearyl alcohol); lipids (e.g. glycerides, phospholipids); paraffin; etc.

Combinations of the above mentioned materials are also possible.

In a preferred form, the invention provides a pharmaceutical composition as described above which is an eroding matrix formulation, wherein the matrix material is selected from the group comprising polyethylene oxide, hydroxypropyl methyl cellulose and paraffin.

In another preferred form, the said pharmaceutical composition is a non-eroding matrix formulation, wherein the matrix material is selected from the group comprising xanthane and polyvinylchloride.

5 In yet another preferred form, the said pharmaceutical composition is a diffusion-controlled membrane coated formulation, wherein the material for film formation is selected from the group comprising ethyl cellulose, hydroxypropyl methyl cellulose and hydroxypropyl cellulose.

10 In the present context, the term "fluvastatin" comprises both of the pure enantiomers, as well as racemic mixtures.

The water soluble salts of fluvastatin to be used in the compositions according to the invention comprise e.g. the sodium, potassium, ammonium salts. The sodium
15 salt is preferred.

The pharmaceutical formulations according to the invention are useful for lowering the blood cholesterol level in animals, in particular mammals, e.g. humans. They are therefore useful as hypercholesterolemic and anti-
20 atherosclerotic agents.

Consequently, the invention provides in another aspect the use of fluvastatin for the manufacture of a pharmaceutical composition for sustained release, for the treatment of hypercholesterolemia. Preferably, the said composition is selected
25 from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.

In yet another aspect, the invention provides a method for the treatment of hypercholesterolemia comprising administering to a mammal, including man, a
30 therapeutically effective amount of a pharmaceutical composition for sustained

release, comprising fluvastatin. Preferably, the said composition is selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.

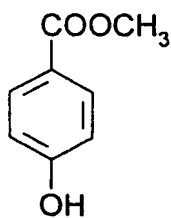
- 5 The pharmaceutical formulations according to the invention can be prepared by use of well known pharmaceutical processing techniques such as blending, granulation, milling, spray drying, compaction, or coating.

The typical daily dose of the active substance fluvastatin varies within a wide
10 range and will depend on various factors such as for example the individual requirement of each patient and the disease. In general, sustained-release dosages will be in the range of 1 to 1000 mg of fluvastatin per day, preferably 2 to 200 mg/day.

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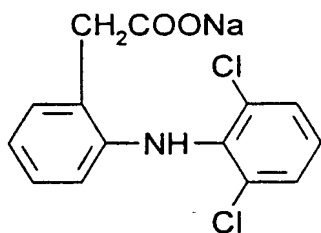
EXAMPLES OF THE INVENTION

To exemplify the unexpectedly favorable properties of fluvastatin in matrix
formulations and membrane coated formulations, the release profile of fluvastatin
20 sodium (water solubility > 50 mg/ml) was compared with two other water soluble drugs, namely methylparaben (methyl p-hydroxybenzoate; water solubility \approx 2 mg/ml) and diclofenac sodium (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monosodium salt; water solubility \approx 5 mg/ml).



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methylparaben



diclofenac sodium

Methylparaben and diclofenac sodium could be expected to exhibit a somewhat slower release rate and longer duration of release, due to the lower water
5 solubility. However, unexpectedly, the release of fluvastatin was consistently slower than methylparaben and diclofenac sodium for all the tested types of sustained-release formulations.

In the following Examples 1 to 3, drug release from various types of tablets was
10 determined in pH 6.8, +37°C, by use of an USP II apparatus at a paddle stirring rate of 75 rpm. All tablet formulations were manufactured by conventional techniques and, for each example, in an identical manner except for the drug constituent.

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EXAMPLE 1: Drug release and tablet erosion for eroding polyethyleneoxide (PEO) matrix tablet.

Fluvastatin or methylparaben (10 mg each) were formulated in an eroding matrix
20 of PEO 8,000,000 (58 mg) and magnesium stearate (0.7 mg). Tablet erosion was determined by weighing after removal of the tablets from the dissolution apparatus and drying to constant weight.

The results (Fig. 1) show that release of fluvastatin from the sustained release
25 tablet was slower than the release of methylparaben in spite of the higher solubility. The tablet erosion and drug release was almost identical for fluvastatin

whereas for the methylparaben tablet, as could be expected for a water soluble drug, the drug release was faster than the tablet erosion. This was a further indication that fluvastatin has unexpectedly favourable extended release properties when administered as an eroding matrix tablet both compared to what
5 could expected from tablet erosion data and compared to another somewhat less soluble drug.

EXAMPLE 2: Release from a non eroding high molecular weight xanthane matrix
10 tablet.

Fluvastatin, methylparaben or diclofenac (5 mg each) were formulated in a non-eroding matrix of xanthane (195 mg).

15 The results (Fig. 2) show that release of fluvastatin from the sustained release tablet was slower than the release of both diclofenac and methylparaben despite the higher solubility. This provides an example that fluvastatin has unexpectedly favourable extended release properties when administered as a non-eroding matrix tablet.

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EXAMPLE 3: Release from eroding paraffin matrix tablet and from a conventional (immediate release) hard gelatin capsule

25 Fluvastatin or diclofenac (20 mg each) were formulated in an eroding matrix of paraffin (120 mg), lactose (30 mg), ethyl cellulose (3 mg) and magnesium stearate (1.7 mg). The immediate release capsule was a hard gelatine capsule containing 20 mg of fluvastatin.

The results (Fig. 3) show that release of fluvastatin from the sustained release tablet was slower than the release of diclofenac despite the higher solubility. This provides another example that fluvastatin has unexpectedly favorable extended release properties when administered as a matrix tablet.

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The drug release for the immediate release capsule was almost immediate in contrast to the duration of drug release of more than 10 hours for fluvastatin sustained-release. This result indicates that the unexpectedly slow release for fluvastatin is not a general property for all kinds of oral fluvastatin formulations, but is limited to certain types of sustained release formulations according to the invention.

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EXAMPLE 4: Transport over a diffusion controlling membrane.

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The release rate of fluvastatin sodium and diclofenac sodium was studied over a polymeric membrane from a donor compartment initially containing all drug substance, thus corresponding to a membrane coated formulation containing the active drug, to a receiving chamber which simulated the medium where the drug is released. The release rate was studied at different initial concentrations of the active drug. The solutions (pH 6.8) in the chambers were well stirred and thermostated at +37°C. From the cumulative amount released versus time, the release rates (amount released/ time) were determined as the slopes of the linear parts of the curves obtained at steady state. No accumulation in the membrane was found of any of the drugs. The results are presented in Fig. 4 as the release rates versus the concentrations used in the experiments.

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The release rate of diclofenac increased as expected when the concentration of diclofenac was increased in the donor chamber. However, surprisingly the release rate of fluvastatin was independent of the concentration of fluvastatin in the donor

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compartment, resulting in a release rate of fluvastatin that was much slower compared to diclofenac. This strengthens that an unexpectedly slow release rate can be maintained for fluvastatin in such formulations irrespective of the amount of dissolved drug within a membrane coated formulations.

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EXAMPLE 5: Manufacture of pharmaceutical formulations

5.1.

- 10 A dosage form adapted, designed and shaped for the oral delivery of fluvastatin sodium to a patient in need of fluvastatin therapy is manufactured as follows: first 30.0 g of fluvastatin sodium, 90.0 g of paraffin, 50.0 g calcium carbonate and 20.0 g sorbitol are screened through a 1.0 mm screen. The screened material are mixed in a planetary mixer for 10 minutes to produce a homogenous blend. Then, a
- 15 granulation solution is prepared by dissolving 2.0 g ethyl cellulose (10 cps) in 150.0 g 95% ethanol during constant stirring for 6 hours. The granulation solution is slowly added to the dry mixture during agitation, to yield a wet granulation. The granulation is dried at +50°C for 12 hours. After drying, the granulation is passed through a screen of 1.5 mm. Magnesium stearate (2.0 g) is mixed in to the
- 20 granulate for 3 minutes. Then, 8 mm round tablets, each comprising 30 mg of fluvastatin sodium are compressed in a Korsch[®] press under a pressure of 25 kN.

5.2.

- 25 Fluvastatin sodium (20.0 g), 150.0 g of hydroxypropyl methyl cellulose (molecular weight 30,000), 30.0 g of sorbitol, 30.0 g of sodium aluminium silicate are dry mixed in a planetary mixer for 5 minutes. Then, a granulation solution is prepared by dissolving 10.0 g of polyvinyl pyrrolidone (molecular weight 360,000) in 200 g of 99.5% ethanol. The granulation solution is slowly added to the dry mixture during agitation, to yield a wetted mass. The granulation is dried overnight at
- 30 +60°C. Next, the granulation is milled in a oscillating granulator through a screen

of 0.7 mm. Magnesium stearate (2.0 g) is mixed with the granulation for 2 minutes. Then, extended release round 10 mm tablets are prepared by compressing the composition with a 30 kN compression force. This fluvastatin tablet comprises 20 mg of fluvastatin sodium.

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5.3.

Fluvastatin sodium (10 g), 50 g of 8,000,000 molecular weight polyethylene oxide, 50 g lactose are dry mixed. Then, 60 g of 99.5% ethanol and the dry mixture are slowly mixed together in a planetary mixer for 5 minutes. The granulate is dried
10 for 12 hours in +45°C. Next, the granulation is passed through a 1.0 mm screen. 1.0 g of magnesium stearate is mixed with the granulation for 2 minutes. Then, extended release round 8 mm tablets are prepared by compressing with a 20 kN compression force. This fluvastatin tablet comprises 10 mg of fluvastatin sodium.

15 5.4.

Fluvastatin tablets is manufactured as follows: first, 3 g of fluvastatin sodium, 20 g of 30,000 molecular weight hydroxypropyl methyl cellulose, 10 g of sodium aluminium silicate and 0.2 g carboxypolymethylene are dry mixed. Then, a granulation solution is prepared by dissolving 2.0 g ethyl cellulose (10 cps) in 20.0
20 g 99.5% ethanol. The granulation solution is slowly added to the dry mixture during agitation, to yield a wet granulation. The granulate is dried for 12 hours in 45°C. Next, the granulation is passed through a 1.0 mm screen. Sodium stearyl fumarate (0.8 g) is mixed with the granulation for 2 minutes. Then, extended release round 11 mm tablets are prepared by compressing with a 25 kN
25 compression force. This fluvastatin tablet comprises 20 mg of fluvastatin sodium.

5.5.

After the initial forming of beads containing fluvastatin sodium, the beads obtained are coated with the polymeric layer controlling the release from the
30 pellet, example of this coating is described below. The polymeric mixture is

dissolved in an organic solvent such as ethanol, isopropyl alcohol and/or methylene chloride. The spraying can be carried out in a coating pan, but is preferably carried out in a fluidized bed.

5	Fluvastatin sodium	300 g
	Methylene chloride	2000 g
	Ethanol 99.5%	1000 g
	SiO ₂ (0.15-0.25)	100 g
10	Polymeric layer	
	Ethyl cellulose 10 cps	65.0 g
	Hydroxypropyl methyl cellulose	15.0 g
	Acetyltributyl citrate	9.0 g
	Methylene chloride	1500 g
15	Isopropylic alcohol	350 g

A solution is prepared by dissolving fluvastatin sodium in 99.5% ethanol and methylene chloride, the solution is then sprayed onto the cores of silicon dioxide in a fluidized bed. 100 g of the beads (fraction 0.4-0.65 mm) are covered with the
20 polymeric layer containing ethyl cellulose 10 cps, hydroxypropyl methyl cellulose and acetyltributyl citrate by spraying a solution of the mentioned substances in methylene chloride and isopropylic alcohol. The coated beads are then filled into hard gelatin capsules.

CLAIMS

1. A pharmaceutical composition for sustained release, said composition comprising a water soluble salt of fluvastatin as active ingredient and being
5 selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.
2. A pharmaceutical composition according to claim 1 wherein the said water soluble salt of fluvastatin is the sodium salt.
- 10 3. A pharmaceutical composition according to claim 1 or 2 which is an eroding matrix formulation.
4. A pharmaceutical composition according to claim 3 wherein the matrix
15 material is selected from the group comprising polyethylene oxide, hydroxypropyl methyl cellulose and paraffin.
5. A pharmaceutical composition according to claim 1 or 2 which is a non-eroding matrix formulation.
- 20 6. A pharmaceutical composition according to claim 5 wherein the matrix material is selected from the group comprising xanthane and polyvinylchloride.
- 25 7. A pharmaceutical composition according to claim 1 or 2 which is a diffusion-controlled membrane coated formulation.
8. A pharmaceutical composition according to claim 7 wherein the material for
30 film formation is selected from the group comprising ethyl cellulose, hydroxypropyl methyl cellulose and hydroxypropyl cellulose.

9. A pharmaceutical composition according to any one of claims 1 to 8 for use in the treatment of hypercholesterolemia.
- 5 10. The use of a water soluble salt of fluvastatin for the manufacture of a pharmaceutical composition for sustained release, for the treatment of hypercholesterolemia.
- 10 11. The use according to claim 10 wherein the said pharmaceutical composition is selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.
- 15 12. A method for the treatment of hypercholesterolemia comprising administering to a mammal, including man, a therapeutically effective amount of a pharmaceutical composition for sustained release, comprising a water soluble salt of fluvastatin.
- 20 13. A method according to claim 12 wherein the said pharmaceutical composition is selected from the group comprising matrix formulations, diffusion-controlled membrane coated formulations; and combinations thereof.

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Fig. 1

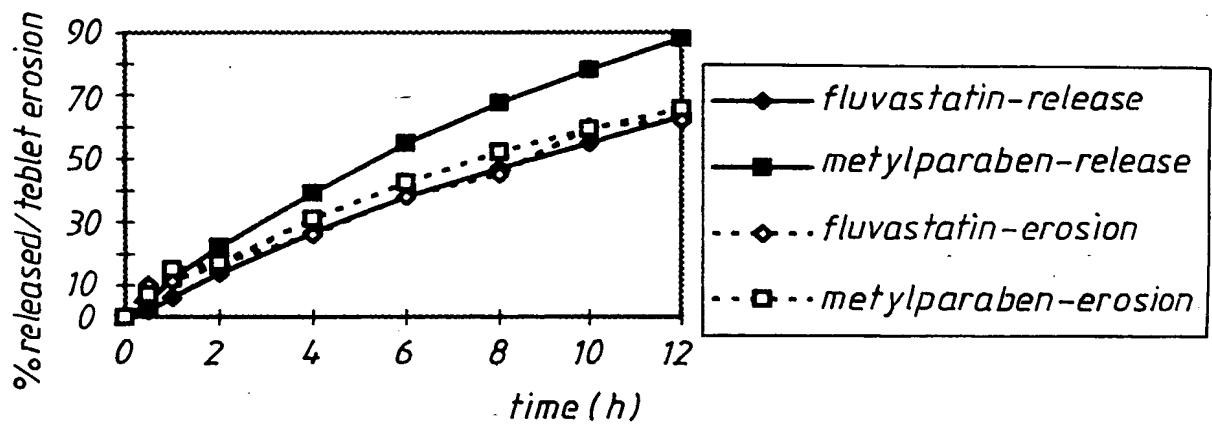
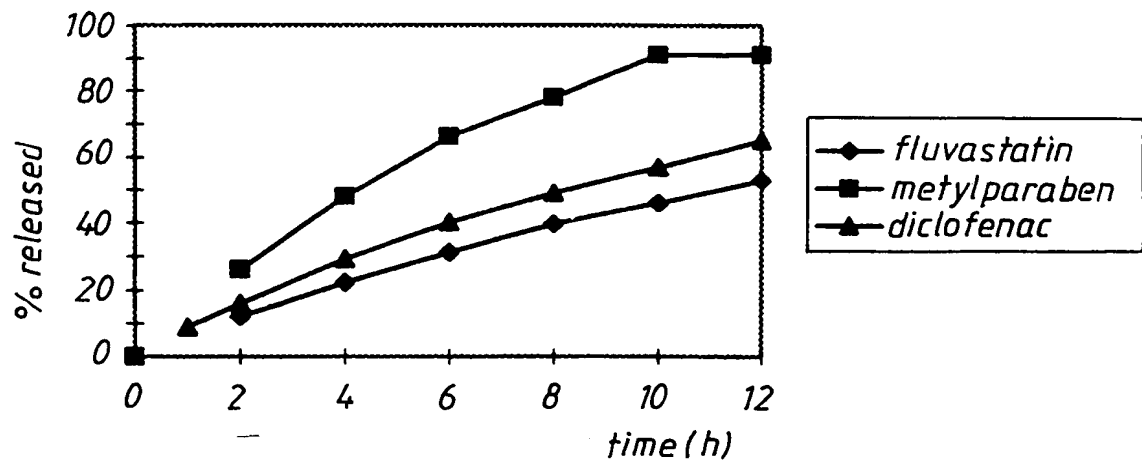


Fig. 2



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Fig. 3

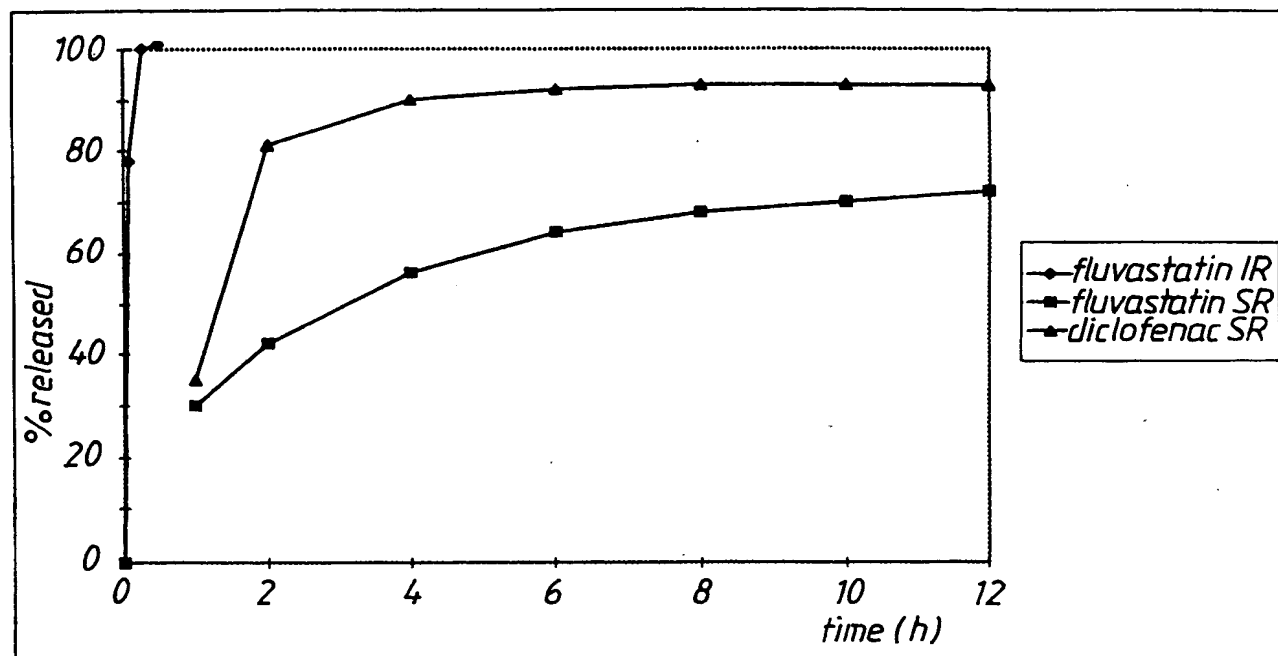
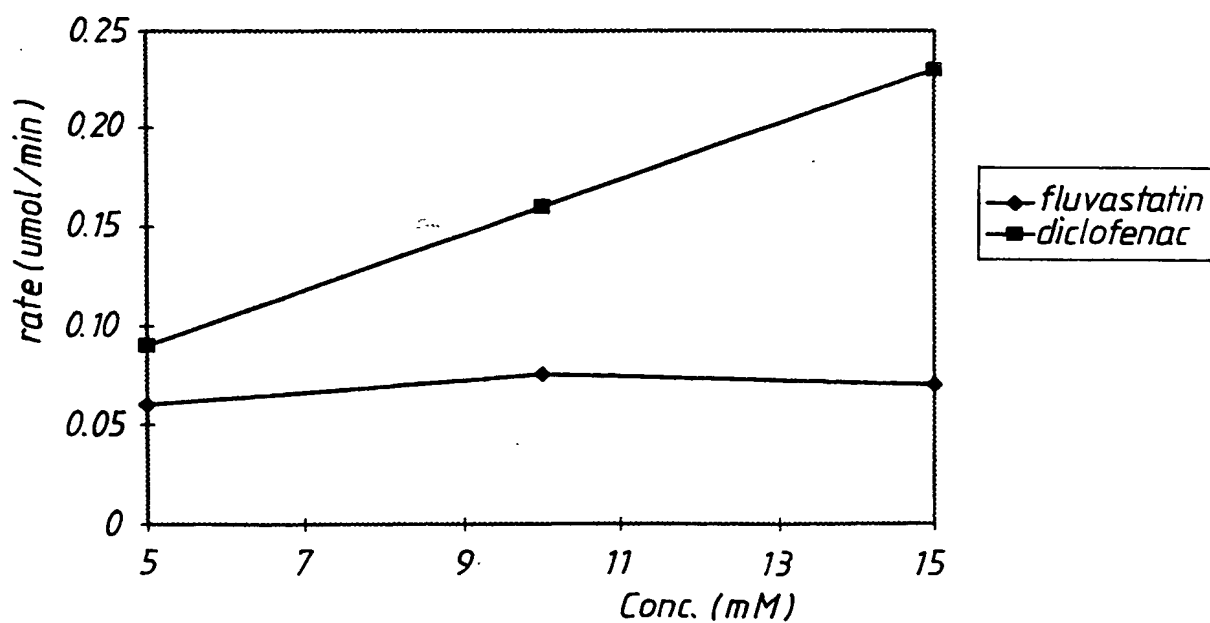


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01604

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: A61K 9/20, A61K 31/19 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EMBASE, MEDLINE, WPI, CAPLUS, CLAIMS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5356896 A (MOHAN B. KABADI ET AL), -18 October 1994 (18.10.94), column 4, line 28 - column 5, line 40 --	1-13
A	EP 0465096 A1 (MERCK & CO. INC.), 8 January 1992 (08.01.92) -- ----- ...	1-13
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search		Date of mailing of the international search report
2 February 1998		06 -02- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01604

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12-13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 12-13 are directed to methods of treatment of the human or animal body by a therapy method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

07/01/98

International application No.

PCT/SE 97/01604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5356896 A	18/10/94	AT 190595 A	15/05/96
		AT 244992 A	15/05/96
		AT 401870 B	27/12/96
		AT 401872 B	27/12/96
		AU 661075 B	13/07/95
		AU 3006992 A	17/06/93
		CA 2085037 A	13/06/93
		CH 684309 A	31/08/94
		DE 4240430 A	17/06/93
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